UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/339,818	06/25/1999	MARK E. DAVIS	038134-50010	3090

28120 7590 09/17/2003

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER
CRANE, LAWRENCE E

ART UNIT	PAPER NUMBER
1623	36

DATE MAILED: 09/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/339,818	Applicant(s) Davis et al.	
	Examiner L. E. Crane	Group Art Unit 1623	

- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **--3--** MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less that thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall ,by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

Status

[X] Responsive to communications filed on **-04/28/03** (amdt G), **06/18/03** (RCE) & **06/26/03**(Sup. Response)-.

[] This action is **FINAL.**

[] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

[X] Claims **---1-3, 6-10, 18, 24-26, 30-34, 44, 46, and 58-64---** are pending in the application. Claim -**27** - has been cancelled.
Of the above claim(s) ---[]--- is/are withdrawn from consideration.

[] Claim(s) ---[]--- is/are allowed.

[X] Claims **---1-3, 6-10, 18, 24-26, 30-34, 44, 46 and 58-64---** are rejected.

[] Claims ---[]--- are objected to.

[] Claim(s) ---[]--- are subject to restriction or election requirement.

Application Papers

[] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[X] The proposed drawings, filed on **-05/02/02-** are [X] approved [] disapproved.

[] The drawing(s) filed on -[]- is/are objected to by the Examiner.

[] The specification is objected to by the Examiner.

[] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

[] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).

[] All [] Some* [] None of the CERTIFIED copies of the priority documents have been
[] received.
[] received in Application No. (Series Code/Serial Number) -[]-.
[] received in the national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: -[]-.

Attachment(s)

[] Information Disclosure Statement(s), PTO-1449, Paper No(s). --[]--
[X] Notice of Reference(s) Cited, PTO-892
[] Notice of Draftsperson's Patent Drawing Review, PTO-948
[] Interview Summary, PTO-413; PN's []
[] Notice of Informal Patent Application, PTO-152
[] Other: -[]-.

Claim **27** has been cancelled, claims **1, 3, 6, 9-10, 24, 30-34, 44 and 45** have been amended, no amendments to the disclosure have been requested, and new claims numbered 47-53*, and now renumbered claims **58-64** under the authority of 37 CFR §1.126, have been added per the amendment filed April 28, 2003. A second declaration under 37 C.F.R. §1.131 filed April 28, 2003 has been entered and considered during the preparation of the instant Office action. A supplemental response, filed June 26, 2003, has also been received and made of record. In order to insure that no further communications had been submitted, examiner called Attorney Matthew Vincent on September 8, 2003. Mr. Vincent, on behalf of Attorney Halstead and following a search of the computer record, assured examiner that the June 26, 2003 communication was the most recent submission in the instant case and that no further submissions had been made to date.

* Claim numbers 47-55 and 56-57 were added in the amendments filed 08/01/01 and 10/08/01 and have subsequently been cancelled.

Applicant argues that the substance of the declaration of May 2, 2002 is relevant to the instant case, noting that examiner's previous conclusion in re this declaration and the report cited therein was not entirely responsive. Examiner respectfully disagrees. Examiner notes that the declaration asserts that the report, and in particular the date of the report (blacked out in submitted copy), supports the conclusion that work on the invention was taking place prior to the filing date of the first Kosak application (April 29, 1998). Examiner cannot affirm or deny this conclusion because the date information is missing. Because the date is missing, the relevance of the Hwang report to the instant prosecution is unclear, and will remain unclear, until the date of its submission is supplied, assuming the report is relevant. Because of the absence of a date of submission or, proof that said report was available

to the public or published on a certain date, examiner has not taken the time to further review the reports contents in detail.

Claims **1-3, 6-10, 18, 24-26, 30-34, 44, 46 and 58-64** remain in the case.

Claims **6** (line 16) **and 30** (line 16) are objected to because of the following informalities:

In the noted claims, the members of the Markush groups being listed therein are not separated by the appropriate (-- , --) punctuation in each instance.

Claim **24 is** objected to because of the following informalities:

In claim **24** at lines 3-4, the terms "cyclodextrin monomer precursor" and "cyclodextrin comonomer precursor" (emphais added) are different but appear to be referring to the same subject matter. See also claim **25** and all other claims dependent from claims **24 and 25**.

Appropriate correction is required.

Claims **1-3, 6-10, 18, 24-26, 30-34, 44, 46 and 58-64** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims have not met the written description standard of Regents of the University of California v. Eli Lilly (119F.3d 1559 at 1568; 43 USPQ2d 1398 at 1406 (Fed. Cir 1997)): see MPEP §2163 at page 2100 et seq. Applicant is requested to note that examiner has carefully

reviewed the examples of the disclosure, particularly Examples 5, 6, 7, 8, 9, 10, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24, and has noted in particular the repeated allegations similar to that found in Example 5 at page 31 which is quoted in part as follows: "[GPC] Fractions were analyzed by GPC and appropriate fractions were lyophilized to yield ... as a ... solid." Examiner found on reference to NMR (Ex. 17) but has failed to find any analytical data establishing molecular weight, elemental composition or mass spectra before and after the selection of the "appropriate fractions" in any synthesis of any water soluble cyclodextrin within the noted Examples. Examiner has also failed to find any examples wherein a complete detailed description of any single GPC purification protocol, or GPC analysis protocol, or both, has been presented. Because complete details of the GPC separation/analysis processes are necessarily critical to isolation and identification of the instant claimed products, the instant disclosure is deemed lack an adequate written description, i.e. to be incomplete, without same. Because no other analytical data has been presented as part of the synthesis of any cyclodextrin oligomer/polymer, there are no factual bases presently to be found within the disclosure which would permit the ordinary practitioner to otherwise infer the requisite details of the GPC protocols in the course of routine experimentation directed to reproducing the isolation of the particular products claimed herein. Similar criticism applies to examples like Example 19 at pages 45-46 wherein "lyophilization" is cited as the purification procedure, but the particular details of how applicant practiced same are not provided.

Applicant's arguments with respect to claims **1-3, 6-10, 18, 24-27, 30-34, 44 and 46** have been considered but are deemed to be moot in view of the new grounds of rejection.

Claims **1-2, 7-10, 18, 24-26, 31-34, 44, 46 and 58-64** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in In re Wands (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims as defined by the generic terms "water-soluble, linear cyclodextrin copolymer," "co-monomer," "cyclodextrin monomer precursor," and "cyclodextrin comonomer precursor," and by process limitations including "comonomer A capable of displacing said leaving groups," is clearly excessive in light of the failure to further define the particular structures of the cyclodextrins being referred to, and the structures of the particular comonomers "A" being referred to as well as which -particular functional groups of said "A" which are expected to react with the leaving groups of the cyclodextrin.

B. The nature of the invention is directed to cyclodextrin copolymers, methods of making same, a composition comprising a cyclodextrin copolymer and a therapeutic agent, and methods of using same to effect improved delivery of pharmaceutically active substances to a particular target within a host in need thereof.

C. The state of the prior art is well known, as established by the Kosak patent and application and other patent references cited herein which themselves by their disclosures and by the references cited therein reveal that cyclodextrins have been in use for some time for purposes similar to those claimed herein.

D. The level of one or ordinary skill is high because the body of knowledge noted above which is directed to the administration of cyclodextrins and oligomers/polymers thereof acting as carriers of pharmaceutically active substances and other substances is well established for certain cyclodextrin-containing structures which differ from those claimed herein.

E. The level of predictability in the art is fairly high in light of the large quantity of prior art noted above.

F. The amount of direction provided by the inventor is limited to the chemical identities, reaction conditions, and quantities of starting materials, but is incomplete because in each and every synthetic example there is no complete description of the isolation procedures carried out to effect the isolation of any particular cyclodextrin oligomer or polymer. In addition, the complete absence of other analytical data (NMRs, mass spectra, molecular weight determination, microanalysis for C,H,N,S and other elements, etc.) renders the ordinary practitioner clueless concerning the particular portions of the product mixture isolated and/or the chemical identities of the species contained therein, particularly when low yields are reported.

G. The existence of working examples are limited in scope, the examples being directed to capped cyclodextrins and the di-iodo and diamino cyclodextrins produced therefrom. Applicant has only

disclosed how to make oligomer/polymer mixtures made from the noted diaminocyclodextrins using specific and well known in the art bifunctional reagents.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive for the following reasons:
i) the particular oligomer/polymer mixtures which have been generated by applicant are not entirely identified because the isolation/purification procedures have not been fully disclosed;
ii) the claims are generic to a vast array of possible cyclodextrin co-oligomer/co-polymers mixtures but applicant has failed to provide guidance concerning how these alternatives are made or what their properties are; and
iii) because applicant has not made most of the compounds encompassed by the overly broad claims found herein, it is not possible for applicant to have provided guidance concerning how to use these un-made cyclodextrin compounds in the preparation and administration of therapeutic compositions, or to have demonstrated with even a single example the alleged improved method of delivery of a pharmaceutically active agent was realized in a host in need thereof.

Applicant's arguments with respect to claims **1-3, 6-10, 18, 24-27, 30-34, 44 and 46** have been considered but are deemed to be moot in view of the new grounds of rejection.

Claims **1-2, 7-10, 18, 24-27, 31-34, 44, 46 and 58-64** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims **9, 10 and 31** the term " whereby said ligand allows the therapeutic agent to target or bind to a cell " lacks proper antecedent basis in claim **1**.

In each of claims **1-2, 7-10, 18, 24-27, 31-34, 44 and 46-53** functional terminology is present which describes chemical functionalities of a "cyclodextrin"-containing species or a "comonomer A," but fails to further define same in sufficient detail to permit one of ordinary skill to be able to determine the particular chemical species being referred to. For example, in claim **1** the terms "water soluble" and "linear" modify the term "cyclodextrin copolymer," but fail to define what particular chemical functional groups and chemical linkages are present between the cyclodextrin and comonomer A. The chemical structure or structures of "comonomer A" is/are not defined in any way in claim **1**. In claim **24** precursors to the polymer are defined as being disubstituted ("cyclodextrin comonomer precursor") and "comonomer A" is described as being "capable of displacing said leaving groups to form a linear cyclodextrin copolymer having repeating groups ... ." Claim **25** defines the cyclodextrin reactant, but is incomplete for failure to define structural identity of the chemical crosslinkers (comonomer A) which are needed to produce the product. Claim **31** adds a "ligand" attachment step, but fails to define a chemical reagent for effecting such a step. Claim **32** narrows the subject matter slightly, but fails to define what "aminating reagent" or "reagents" are converting the di-iodocyclodextrins of claim **25** to "diamino" analogues. Claim **58** is directed to reacting a "cyclodextrin derivative modified to bear one reactive site at each of exactly two positions," suggesting that either valence rules are being violated, or that applicant has not clearly described the subject matter. Similarly, claim **58** is directed to a "linker" which has "exactly two reactive moieties capable of forming a

covalent bound with the reactive the reactive sites [of the cyclodextrin derivative]under polymerization conditions," but has failed to define the chemical identity or identities of the "reactive moieties" or the particular "polymerization conditions" being referred to. See also claim **61**. See also compound claims **59, 60 and 62-64** which have the same or similar problems following from reliance on functional terminology.

Applicant's arguments with respect to claims **1-3, 6-10, 18, 24-27, 30-34, 44 and 46** have been considered but are deemed to be moot in view of the new grounds of rejection.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> "A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."
>
> (e) the invention was described in a patent granted on an application to another filed in the United States before the invention thereof by applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent."

Claims **1-3, 7, 59-60 and 62-64** are rejected under 35 U.S.C. §102(**b**) as being anticipated by **Aldrich Catalog/Handbook of Fine Chemicals, 1994-1995** (PTO-892 ref. **XA**).

Applicant is referred to the circled entry from page 399 which anticipates the instant claims.

Applicant's arguments with respect to claims **1-3, 6-10, 18, 24-27, 30-34, 44 and 46** have been considered but are deemed to be moot in view of the new grounds of rejection.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **1-3, 7-10, 24-26, 31-32 and 58-64** are rejected under 35 U.S.C. §102(**e**) as being anticipated by, or alternatively under 35 U.S.C. §103(**a**) as being unpatentable over the **Kosak '921** patent application (PTO-892 ref. **F**).

The instant claims are directed to copolymers comprising cyclodextrins and various bifunctional linkers, the copolymer being further optionally derivatized with biologically active ligands; methods of making the copolymer, ligand-equipped copolymer, and complexes with active pharmaceutical agents; and a method of delivering pharmaceuticals therewith.

Kosak '921 at pages 30-31 (Preparation 1) discloses a process of making water-soluble copolymers of cyclodextrins and 1,4-butanediol diglycidyl ether (BDE) made by mixing the desired cyclodextrin with BDE in the presence of hydroxide ion. Additionally the reference describes how the product of the polymerization may be further modified by treatment with lysine (p. 31-32)to produce amino groups which may be

subsequently reacted with ligands or other labels. Guests molecules are disclosed generically by Kosak '921.

Although **Kosak '921** fails to provide the guidance of specific di-functionalized cyclodextrins, the products disclosed by this reference must include cyclodextrins coupled in a "linear" manner by BDE linkers/comonomers; i.e. two BDE linkages per cyclodextrin and 2-cyclodextrin linkages per BDE linker on the average. Although the **Kosak '921** polymer is not prevented during preparation from including branched portions, it still reads on the instant claims, because the instant claims have relied on the term "comprising" {including} the presence of which permits the presence of non-conforming (non-linear) portions in its own product as well as in the Kosak '921's cyclodextrin/BDE polymers. In addition, according to the 1997 edition of McGraw-Hill Dictionary of Chemistry's definition, the term "leaving group" does not entirely exclude the departure of protons during a chemical process.

Therefore, the instant claimed cyclodextrin/comonomer copolymers, methods of making, pharmaceutical compositions thereof, and methods of pharmaceutical delivery therewith are either anticipated by the **Kosak '921** reference, or where not anticipated, would have been obvious to one of ordinary skill in the art having the above cited reference before him at the time the invention was made.

Applicant's arguments with respect to claims **1-3, 6-10, 18, 24-27, 30-34, 44 and 46** have been considered but are deemed to be moot in view of the new grounds of rejection.

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must

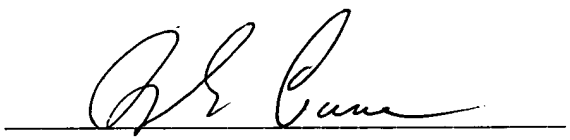
conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at (703)-308-4624.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235**.

LECrane:lec
09/08/03



L. E. Crane, Ph.D. JD
Patent Examiner
Technology Center 1600